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Does chronic high-intensity endurance training have an effect on cardiovascular markers of active populations and athletes? Systematic review and meta-analysis

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ABSTRACT

Objective The objective of this study was to ascertain the effects of high-intensity chronic endurance training on cardiovascular markers of active populations and athletes.

Methods This review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We used databases of PubMed, Science Direct, SPORTDiscus, Google Scholar and grey literatures with Mesh and free-text search as well as manual searches to identify relevant studies from June 2017 to September 2019. Weighted standardised mean differences and effect size of the intervention group versus the control group were calculated using a random effect model with 95% CI.

Result There was significant improvement in high-density lipoprotein with weighted standardised mean difference and effect size=−1.06 (−1.83 to −0.30), p=0.006. We have also observed a significant reduction in low-density lipoprotein and total cholesterol with weighted standardised mean difference and effect size=−0.97 (−1.58 to −0.36), p=0.002, and = −0.78 (−1.34 to −0.22), p=0.007, respectively. There was a significant reduction in interleukin 6 (IL-6) using a fixed effect model with weighted standardised mean difference and effect size=−0.87 (−1.33 to −0.40), p=0.0003 and C reactive protein (CRP) with weighted standardised mean differences and effect size=−0.41 (−0.73 to −0.09), p=0.01.

Conclusion Chronic high-intensity endurance training improves healthy lipid profiles (increase high-density lipoprotein, decreased low-density lipoprotein and total cholesterol). And decreased inflammatory markers (IL-6 and CRP) independent of age and sex and cannot be associated with an increased risk of developing cardiovascular disease.

PROSPERO registration number CRD 42017081369.

Strengths and limitations of this study

- We used a systematic and comprehensive search strategy which resulted in an inclusive list of studies.
- We applied the Cochrane Risk of Bias Tool to assess the risk of bias from individual studies.
- We conduct the sensitivity analysis to test whether the conclusions are robust.
- We did not conduct subgroup analysis across age groups.
- The literature search was limited to articles published in English only because the authors did not have the resources to translate articles written in other languages.

INTRODUCTION

Regular endurance exercise is part of a healthy lifestyle associated with reduced cardiovascular disease (CVD) risk.[1] Most studies observing CVD showed a gradual decrease in CVD risk with progressively more exertion of the intensity. Even doses as low as 15 min of physical activity per day seem to reduce CVD risk and all causes of mortality.[2] Higher intensity endurance training has also been reported with further reduced mortality risks, with the most active individuals demonstrating the best overall life expectancy.[2 3] However, recent evidence suggests that such intense exercise may actually increase CVD risk and not associated with better survival.[4 5] Pheidippides was the first marathon runner exposed to sudden death in his 40 years old age during the Greco-Persian War in 490 BC. He collapsed after he runs 150 miles during the first 2 days and 26 miles during the third day from a battlefield near Marathon to Athens to deliver news of Greek victory.[6 7] Now after 2500 years with the rise in popularity of endurance sports, athletes are exposed to adverse cardiac structural remodelling, and predispose to acute and chronic CVD problems.[8] The rate of sudden cardiac death (SCD) among marathoners is approximately 1 per 100 000–200 000 participants[9]

and doubled in triathlon competitors.[10] On the other hand, the mortality rate has increased as the number of participants increased. These deaths are caused by unsuspected CVDs.[11] High-intensity exercise might have harmful effects on cardiac health by potentially generating myocardial fibrosis[12] and exacerbated to arrhythmias[13] and SCD. The hypothesis for such a pathological adaptation is emerging and is based largely on medical evidence.

CVDs, such as atrial fibrillation[14] and coronary artery calcification in apparently healthy male athletes above 55 years old,[15] have been reported in response to high-intensity endurance exercise and marathon running. Furthermore, chronic excessive endurance exercise may cause adverse physiological and morphological cardiac adaptations, particularly in the continuously growing middle-aged amateur runners.[16] Previous animal studies have also found that acute adverse cardiac effects have been observed in endurance exercise.[17] Besides, a study of runners, those run less, up to 20 miles per week received a mortality benefit while those that run more than 20 miles per week did not gain significant additional health benefits.[18] It would appear that a U-shaped relationship between exercise intensity and risk form training, where moderate-to-high intensity gained benefit, but inactivity and more extreme intensity may not always be beneficial.[19]

The prescription of endurance training is usually based on different levels of exercise intensity zones.[20] However, the intensity level and duration of physical activity required to alter cardiovascular function and to reduce CVD risks are not yet defined. Training performed below a certain threshold intensity will have no hormonal response unless with a certain long duration.[21] Training intensity and duration are crucial in causing hormonal changes as well as to trigger acute and chronic adaptation or to avoid overload.[22] However, much remains uncertain regarding the effects of chronic high-intensity endurance training on CVD biomarkers for targeted interventions and clinical evaluations.[23 24] Moreover, different studies revealed various results in response to chronic high-intensity endurance training. Accordingly, we aimed to perform a meta-analysis in order to provide a statistical summary of comparable studies as a means to consolidate a quantitative review of the effects of chronic high-intensity endurance training on cardiovascular markers. Therefore, the aim of this systematic review and meta-analysis was to assess the effects of chronic high-intensity endurance training on cardiovascular markers of active individuals and athletes', that is, inflammatory and lipoprotein markers. Thus, we hypothesised that chronic high-intensity endurance training might have no adverse effect on cardiovascular markers of active individuals and athletes.

METHODS

Search strategy

A literature search was conducted from June 2017 to September 2019. The following databases were searched:

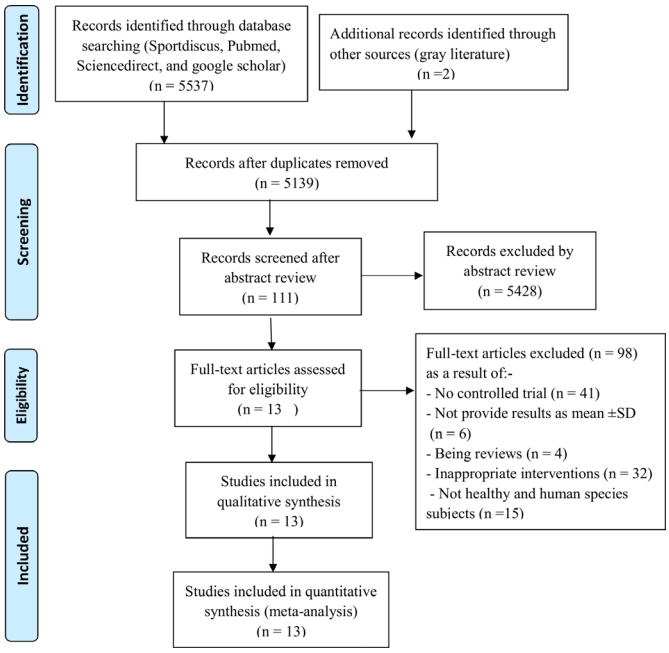


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study identification and selection process.

PubMed, Science Direct, SPORTDiscus, Google Scholar with Mesh and free-text search and grey literatures with manual search. Abstracts and citations from scientific conferences were excluded. This review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[25 26]

The three independent authors reviewed the studies at every stage and duplicates are managed together according to PRISMA flow diagram figure 1. Then decided whether inclusion is appropriate. Any disagreements between the three investigators were resolved by consensus to determine the inclusion of the study.

Eligibility criteria

Studies were eligible for inclusion in this review if: (1) the study included only healthy subjects; (2) studies observed high-intensity training above 70% HR max or above 70% VO_2max training protocol; (3) studies seen endurance training done more than 7 weeks; (4) the study compares the outcomes of intervention group with the control group; (5) cardiovascular markers such as lipid and inflammatory markers were measured; (6) the study observed controlled trials; (7) the articles are published in English language from 1997 to September 2019. Citations out of the above criteria were excluded.

Data extraction

The following data were extracted: the characteristics of the participants in the control and intervention group, that is, sample size, age in mean and SD, the methodology used for endurance training (ie, type of training, intensity and duration), outcomes of cardiovascular markers measured at the end of the intervention like

lipid/lipoprotein markers (ie, total cholesterol (TC), high-density lipoprotein (HDLc), low-density lipoprotein (LDLc)). Inflammatory markers (ie, interleukin 6 (IL-6), and C reactive protein (CRP)).

Data analysis

We estimated outcomes using meta-analysis with random effects and pooled standardised mean difference of the changes of scores for TC, HDLc, LDLc and CRP in addition, fixed effect model for IL-6 using 95% CI. We estimated a pooled standardised mean difference of the final values to avoid effect variation for outcomes that were measured and reported with different scales. We visually inspected funnel plots of the standardised mean difference versus SE and performed Egger's regression asymmetry test to assess bias due to small study effects.[27] Except HDL, there was no indication of small-study effects available from the funnel plots or Egger's test for the rest four outcomes. Statistical heterogeneity between studies was tested using Q statistics and quantified with I^2 statistics.[28] We have also seen the summary effect estimates of each outcome. We did not perform subgroup analysis since our objective is not to observe to which group endurance training has an effect. All the analysis has been done by using review manager software (RevMan V.5.3).

Risk of bias in individual studies

We used the Cochrane Risk of Bias Tool to assess the risk of bias in individual studies.[29] The tool consists of the following seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. Each domain was considered for each of the included studies and the result of the overall risk of bias for each study was assessed and displayed using software RevMan V.5.3.

Sensitivity analysis

We did sensitivity analysis based on the impact of the statistical methods (mean difference or standardised mean difference) to check whether the conclusions would have been different if a different effect size measure had been used. We checked whether conclusions would have been the same if fixed-effect vs random-effect methods had been used. In addition, we did leave-one-out method to check whether the conclusions reached might differ substantially if a single study or a few studies were omitted.[30]

Patient and public involvement

There were no patients' involvement in the development of the research question, and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will not be disseminated to study participants.

RESULT

Study selection

In the search strategy, we identified 5539 articles through online databases and grey literature. After removal of duplicates, 5139 citations were identified and after title and abstract screening 111 articles were included and 5428 were excluded. Out of 111 articles, 35 articles were included and 76 were excluded for full-text review. Out of this, 13 articles were selected for qualitative and quantitative synthesis (meta-analysis). The rest excluded as a result of no controlled trial, not provide results as mean±SD, being reviews, inappropriate interventions, not healthy and human species subjects (figure 1).

Study characteristics

A total of 876 participants in the 13 studies were included, of which 433 experimental and 443 were in the control groups. Studies were published between 1997 and 2017 with English language. Of these, four were conducted in USA,[31–34] two were conducted in Australia,[35 36] one in Germany,[37] one in Scotland,[38] one in Poland,[39] one in Estonia,[40] two in Iran[41 42] and one in India.[43] Three studies recruited only women[31 32 42] and two studies recruited both man and woman.[34 38] The remaining eight studies recruited only male participants.

Age of participants of the study ranged from 16 to 89 years old. From these, three studies included participants with age of 16–22 years old, four studies included participants with age of 22–40 years old,[33 36 37 42] four studies included participants with age of 40–59 years old[31 35 39 40] and the rest two studies included participants with age of 60–89 years old.[34 41]

The participant training experience in included studies varies from sedentary to distance runners; from these, four studies included runners or athletes, three studies included active non-athlete participants,[32 38 39] one study included both athletes and non-athletes,[43] one study included sedentary participants,[33] two studies included overweight participant[36 42] and two studies included elderly and healthy ageing participants.[34 41] Both participates more than 7-week endurance training.

The study protocol of each included study varied in intervention time from 7 weeks to 25 years and in endurance training type. From this, one study intervention was conducted with high-intensity interval training,[35] one study conducted high-intensity intermittent endurance training,[36] and three studies used high-intensity leisure time physical activity intervention.[34 39 42] The remaining eight studies followed high-intensity continuous endurance training; see table 1.

Even though some studies lack specificity, studies done above 70% HR max or above 70% VO_2max and studies used marathon training above 7 weeks included as high-intensity endurance exercise in this systematic review and meta-analysis.

Out of the 13 studies included in quantitative analysis, 10 reported CRP from these, 7 studies reported positive result for high-intensity endurance training adaptation

Table 1 General characteristics of studies included in chronic effects of high-intensity endurance exercise

Author and year	Subjects	Country	Age, years and M±SD	Sample size	Type of exercise	Outcome markers
Mattusch *et al*, 2000[37]	Runners	Germany	25–40	22	9-month college marathon run preparation	CRP
Taylor *et al*, 2014[31]	Marathon runners	Boston, USA	46±13	42	3-month preparation for Boston marathon	CRP, HDL, LDL, TC
Allen *et al*, 2017[35]	Marathon runners	Australia	49.2±6.1	34	9-week high-intensity interval training	CRP
Pihl *et al*, 2003[40]	Endurance athletes	Estonia	48.0±6.1	78	23.1±6.3 years competitive endurance sports	HDL, LDL, TC, CRP
Vance *et al*, 2014[33]	Sedentary men	Miami, USA	22–37	47	17-week half-marathon training	HDL, LDL, CRP
Gokhale *et al*,2007[43]	Athletes and non-athletes	Bangalore, India	18±1.3 and 20+0.6	20	6-month training	IL-6
Heydari *et al*, 2012[36]	Overweight men	Australia	24.7±4.8, 25.1±3.9	46	12-week high-intensity intermittent training	HDL, LDL, TC
Kwaśniewska *et al*, 2016[39]	Leisure time participants	Lodz, Poland	59.7 ±9	62	25-year high-intensity leisure time physical activity (PA)	CRP, IL-6, LDL, HDL, TC
Buchan *et al*, 2011[38]	Students	Scotland, UK	16.4±600.7	57	7-week brief intensive and endurance exercise	CRP, IL-6, HDL, LDL, TC
Dolati *et al*, 2017[42]	Overweight women	Iran	18–45	24	8-week total body aerobic resistance exercise programme	LDL, HDL and TC
Nicklas *et al*, 2008[34]	Elderly	USA	70–89	424	12-month PA intervention With successful ageing	CRP, IL-6
Shahram, 2011[41]	Healthy ageing men	Iran	60–70	24	8-week of endurance training	CRP
Daray *et al*, 2011[32]	Young women	USA	18–24	38	15-week endurance, endurance and resistance	CRP

CRP, C reactive protein; HDL, high-density lipoprotein; IL-6, interleukin 6; LDL, low-density lipoprotein; TC, total cholesterol.

and 3 studies reported that there was no significant change in CRP. Seven studies also reported HDL out of this: four studies reported significant change and three studies did not report significant increase. In addition, seven studies reported LDL from this: four studies not reported a positive result, but the remaining three studies reported a significant reduction. Six studies reported TC out of this: three studies reported positive results, but not the remaining three studies. Four studies reported IL-6 from this: only one study reported positive results and the remaining three studies did not report significant change.

Lipid profile

The findings of this systematic review and meta-analysis on lipoprotein markers (ie, HDL, LDL and TC) showed a significant difference in response to chronic high-intensity endurance training.

High-density lipoprotein

Seven studies with a total of 331 participants of which 159 participants in the intervention group and 172 participants in the control group were included in the analysis of HDL and we estimated a pooled standardised mean difference using a random-effect model. The intervention group showed statistically different result in HDL than the control group in response to chronic high-intensity endurance training with an effect estimate of the standardised mean difference in male^{-1} and 95% CI=−1.06 (−1.83 to −0.30) and p=0.006 (figure 2).

Low-density lipoprotein

Seven studies with a total of 331 participants of which 159 participants in the intervention group and 172 participants in the control group were included in the analysis of LDL and we estimated a pooled standardised mean differences using a random-effect model. The intervention group showed statistically different result in LDL than the control group in response to chronic high-intensity endurance training with an effect estimate of the standardised mean difference in mmol^{-1} and 95% CI=−0.97 (−1.58 to −0.36) and p=0.002 (figure 2).

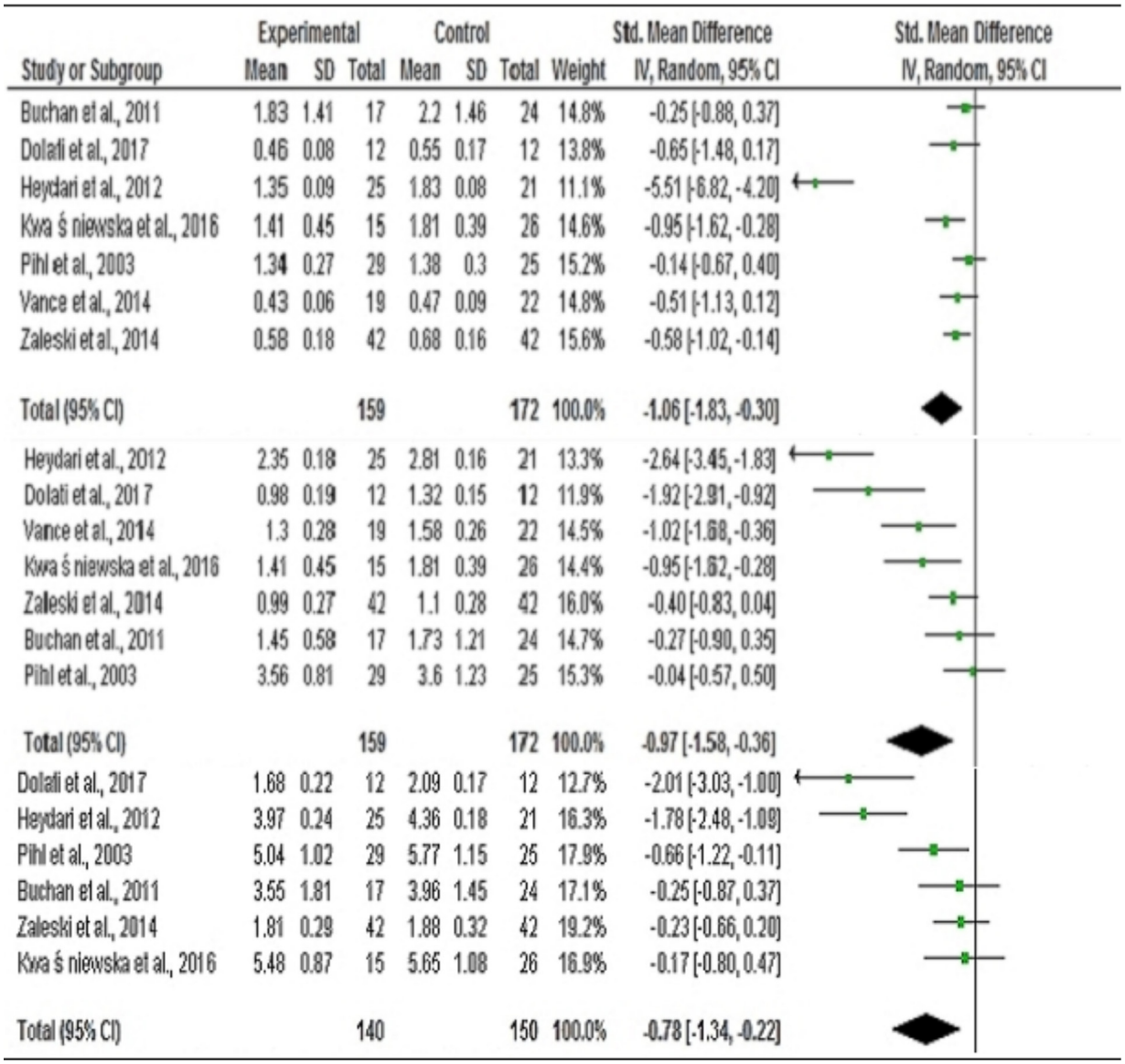


Figure 2 Forest plot for high-density lipoprotein, low-density lipoprotein and total cholesterol.

Total cholesterol

Six studies[31 36 38–40 42] with a total of 290 participants of which 140 participants in the intervention group and 150 participants in the control group were included in the analysis of TC and we estimated a pooled standardised mean difference using a random-effect model. The intervention group showed decrease in TC with statistically significant results than the control group in response to chronic high-intensity endurance training with an effect estimate of the standardised mean difference in $mmol^{-1}$ and 95% CI=−0.78 (−1.34 to −0.22) and p=0.007 (figure 2).

Inflammatory markers

In this meta-analysis in addition to lipoprotein markers, we observed inflammatory marker, that is, CRP and IL-6 and found significantly decreased results in response to chronic high-intensity endurance training.

Interleukin 6

Four studies[34 38 39 43] with a total of 526 participants of which 255 participants in the intervention group and 271 participants in the control group were included in the analysis of IL-6 and we estimated a pooled mean difference using a fixed-effect model. The rationale for using a fixed-effect model to this outcome is since the number of studies is very small, the estimate of the between-studies variance (τ^2) will have poor precision. In this case, we may choose among several options, each of them problematic. Random-effect model is still the appropriate model, but we lack the information needed to apply it correctly. The other option is to report the separate effects and not report a summary effect, but the problem is that some readers will revert to vote counting and possibly reach an erroneous conclusion. Another option is to perform a fixed-effect analysis. This approach would yield a descriptive analysis of the included studies, but would not allow

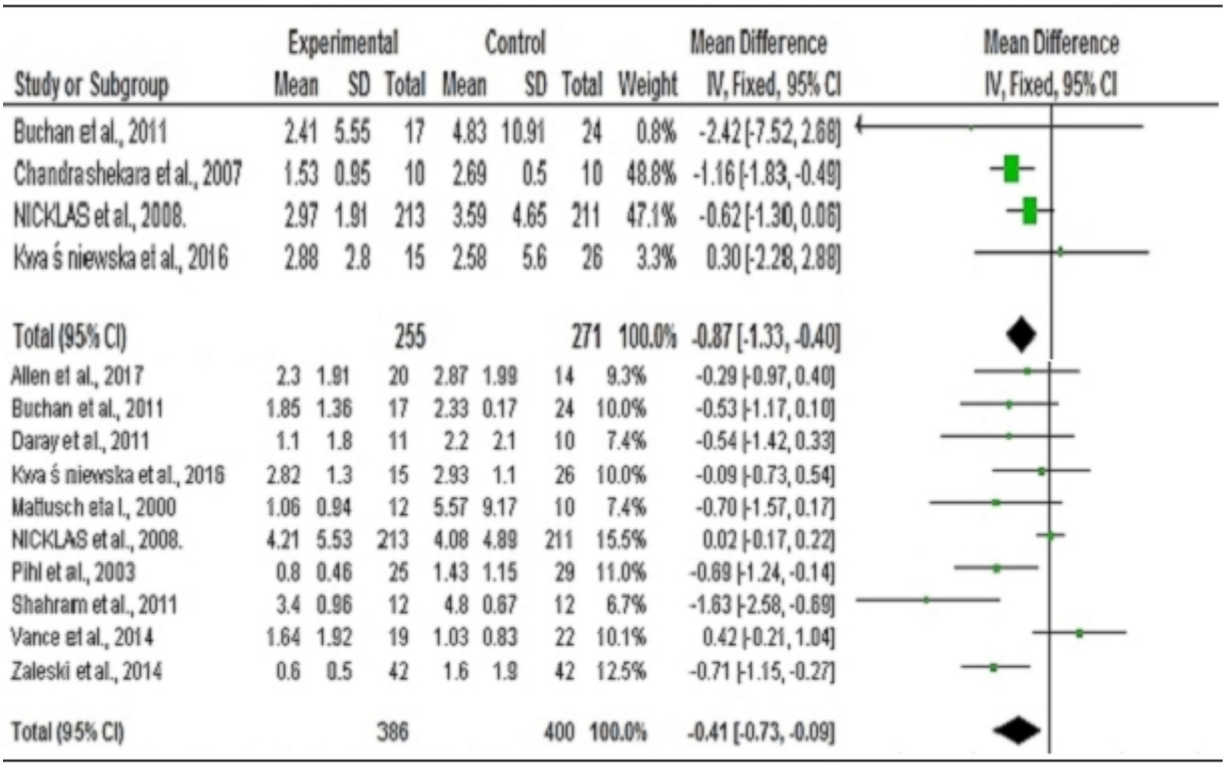


Figure 3 Forest plot for C reactive protein and interleukin 6.

us to make inferences about a wider population. A third option is to take a Bayesian approach where the estimate of (τ^2) is based on data from outside of the current set of studies, but the problem is that we have to be expertise in Bayesian meta-analysis and some researchers have a philosophical objection to this approach.[44] For this reason, we choose to use a fixed-effect model. As a result, intervention group showed statistically significant result in IL-6 than the control group in response to chronic high-intensity endurance training with effect estimate of mean difference in pg/mL and 95% CI=−0.87 (−1.33 to −0.40) and p=0.0003 (figure 3).

C reactive protein

Ten studies[31 33–41] with a total of 786 participants of which 386 participants in the intervention group and 400 participants in the control group were included in the analysis of CRP and we estimated a pooled standardised mean difference using the random-effect model. The intervention group showed a significant decrease in CRP than the control group in response to chronic high-intensity endurance training with an effect estimate of the standardised mean difference in mg/L and 95% CI=−0.41 (−0.73 to −0.09) and p=0.01 (figure 3).

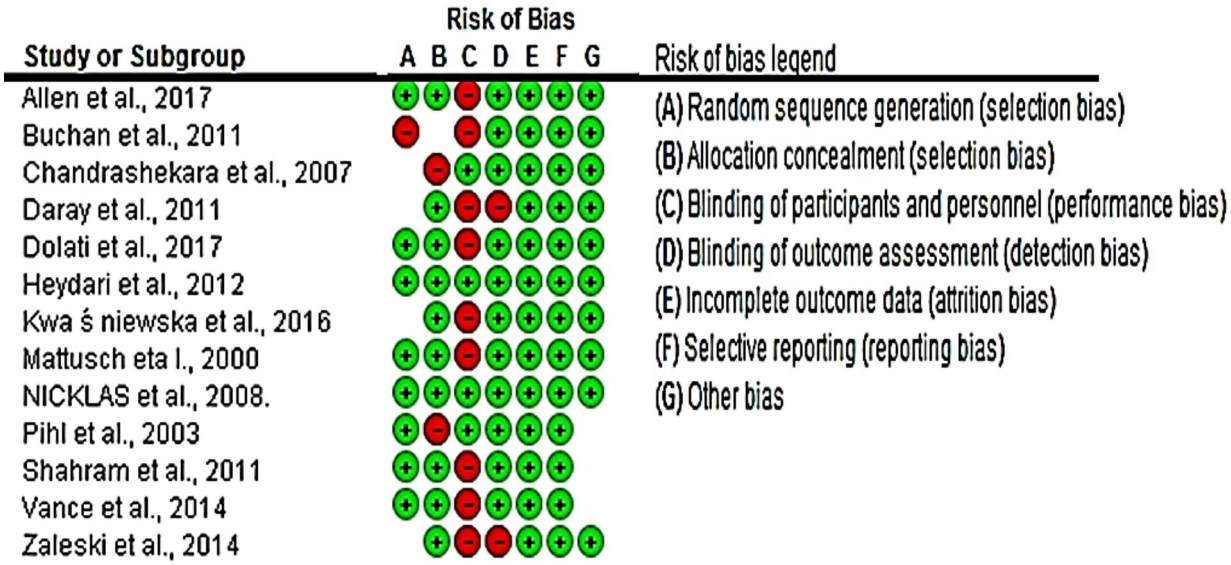
Risk of bias

We assessed the risk of bias for each study, according to the seven domains in the Cochrane Risk of Bias Tool and indicated in figure 4. Challenges we face to assess risk of bias were incomplete reporting by authors where reporting detail made assessment possible. Most bias in the included studies was performance bias or lack of blinding of participants and personnel, which is difficult to manage in an exercise intervention study whereby exercise must be supervised. Two of the included studies have allocation concealment bias,[40 43] one study had selection bias or random sequence generation[38] and two studies have blinding of outcome assessment or detection bias[31 32] which creates difficulties in the outcome assessment (figure 4).

DISCUSSION

The purpose of this meta-analysis was to provide quantitative statistical summary of comparable studies to observe the effects of chronic high-intensity endurance training on cardiovascular markers in athletes and active populations. The main findings of this meta-analysis were lipoprotein markers (ie, HDL, LDL and TC) and inflammatory marker (ie, CRP, IL-6) which showed significantly different results in response to chronic high-intensity endurance training.

Various studies reported that exercise increases the levels of HDL through its lipoprotein expression which were analogous to the results of our meta-analysis.[45] Consistently with the current meta-analysis, studies reported that there was significant increase in HDL and decrease in LDL and TC in response to endurance training.[46] In line with this, our meta-analysis suggested that regular endurance exercise is particularly helpful to improve the lipid lipoprotein profile of men with low HDL cholesterol.[47] We have also observed significant reduction of LDL and TC as a result of chronic high-intensity



Circle With + sign implies low risk of bias and Circles with – sign implies High risk of bias and the free space implies unclear risk of bias.

Figure 4 Cochrane risk of bias assessment for individual studies.

endurance training. Similarly with our result, a meta-analysis that analysed 31 trials reported an overall decrease in LDLc, TC and increase in HDLc as a result of endurance training.[46] Consistently with our study, a meta-analysis by Goldhammer *et al*[48] of 66 controlled trials reported an overall decrease in LDL, TC and with an increase in HDLc.

This meta-analysis revealed that IL-6 showed significantly different results of the experimental group than the controlled one. In line with our result, endurance training in patients with coronary artery disease is an effective means in reduction of IL-6 possibly improving coronary risk profile[49] and it has anti-inflammatory properties and could have acted as an inhibitor of the inflammatory response to exercise.[50] Similarly with our meta-analysis result,[51] after 8 weeks and[52] after 12-week endurance training reported that there were decreases in IL-6. This change in IL-6 serum concentrations in response to long-term exercise training programme may vary from individual to individual due to genetic variations in the IL-6 gene independent of age and gender.[53]

In this meta-analysis, we found a significantly different result in CRP. In agreement with our result, studies reported that there are decreased CRP levels as a result of an adaptation to intense physical exercise by increasing levels of anti-inflammatory cytokines.[50] Similarly, studies reported that endurance training is an effective means in inducing reduction in CRP and reducing coronary risk profile.[49 51] Another studies reported that cytokines (IL-6 and CRP) were independently and inversely associated with a direct measure of cardiorespiratory fitness or VO_2 max[54] indicating that when endurance exercise adapted and cardiorespiratory fitness improved, there will be decreased production of cytokines. Consistently with our result, a study on CRP[55] reported that chronic endurance training reduces resting CRP levels by decreasing cytokine production in adipose tissue, skeletal muscles, endothelial and blood mononuclear cells and by improving endothelial function insulin sensitivity as well as antioxidant effect.

Generally, it is well known that in the majority of endurance athletes' lifelong habit of training and its adaptation will improve cardiovascular morbidity and mortality.[56] Despite the fact that exercise at high relative intensity seems to induce larger beneficial adaptation in the cardiovascular system, it is unknown whether this type of training is safe for predisposed athletes.[57] Consistently with our result, the prospective study from a study of US male physicians suggest that habitual vigorous exercise diminishes the risk of sudden death during vigorous exertion.[58] The absolute magnitude of the increase in risk associated with vigorous exertion is extremely small, and the overall risk of sudden death was not increased in association with increasing frequency of vigorous exercise.[58] Even sometimes, high-intensity endurance training is safe and highly relevant in patients with CVD[59] if there is close monitoring during the training.

CONCLUSION

Generally, the results of the present meta-analysis provide evidence that chronic high-intensity endurance exercise improves healthy lipid profiles (increase HDL, LDL and TC) and decreased inflammatory markers (IL-6 as well as CRP) and it may not be associated with an increased risk of developing CVD. Further investigations should be done on the long-term effects of extremely high-intensity endurance training and genetic predisposition of individuals for cardiovascular problems exacerbated by exercise training based on age and sex differences.

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Contributors All authors were involved in the design and concept of the study. MG involved in the consulting of the design and method of the study as well as in writing the manuscript. SM was involved in consulting the data gathering time and tools. DM was involved in designing theoretical framework of the study and GT involved from the conception to experiment and writing the manuscript. AH was involved in the systematic literature search and data extraction. EH was involved in statistical analysis.

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